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Potential of Thymol as a Natural Solution against the Maize Weevil [*Sitophilus zeamais* (Motsch.)]: *in Vitro*, *In Vivo* and *In Silico* Studies

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Using essential oils (EOs) and their primary compounds to protect stored grains from insect infestations offers a promising alternative to synthetic insecticides. This study tested thymol, a major constituent of thymus EO (*Thymus vulgaris*), for its insecticidal effects on the maize weevil, *Sitophilus zeamais* (*S. zeamais)*. The repellent activity was evaluated using a preferred zone method, where insects were given the choice between treated and untreated areas. This method demonstrated significant repellent effects across all tested concentrations, with repellency rates exceeding 80% at a concentration of 300 µL/mL. In fumigant activity tests, the concentration of 300 µL/mL achieved highly significant results, with a mortality rate of 98% by the fourth day of treatment. Additionally, topical exposure of insects to thymol showed significant insecticidal activity, with mortality rates of 81% and 100% at doses 0.06 and 0.12 µL per insect, respectively. Insects exposed to grains treated with concentrations of 1.2, 1.8, and 2.4 µL/mL exhibited 100% mortality within 7 days. Significant differences were also found between treated and untreated grains for weight loss, hole percentage, and the inhibition of progeny insects, irrespective of the concentration. The molecular docking simulations of thymol against the Acetylcholinesterase protein (PDB ID: 7E3H), showed that thymol interacts strongly with this protein target (binding energy of -7.291 kcal/mol), suggesting potential neurotoxic effects on *S. zeamais.* These findings highlight thymol's potential as a natural and effective alternative to synthetic insecticides for the protection of stored grains against weevil infestations, offering a promising solution for safer post-harvest management.
Keywords: Insecticidal activity, fumigation, repellency, molecular docking, *sitophilus zeamais*, thymol.

INTRODUCTION

Maize (*Zea mays* L.) is one of the world's most widely cultivated cereal crops due to its important role in both human and animal nutrition (Kumar & Jhariya, 2013). However, infestation by insect pests, particularly weevils, poses a major challenge to maize preservation during post-harvest storage. Weevil infestations typically begin in the field just before the crop reaches full maturity (Opiyo et al., 2022), leading to destructive activity during storage. Weevil infestations cause both qualitative and quantitative losses in maize, reducing yields by up to 25% in developed countries and as much as 75% in developing countries (Suleiman et al., 2015; Barau et al., 2020).

The corn weevil, *Sitophilus zeamais* Motschulsky (Coleoptera: Curculionidae), is among the most destructive pests affecting stored maize (Suleiman et al., 2015). Measuring between 2.5 and 4.5 mm in length (Ramlal et al., 2020), females weevils lay their eggs within the grain. Upon hatching, the larvae burrow into the grain to feed (Longstaff, 1981; Ramlal et al., 2020). The complete life cycle, from larvae to pupae to adults, occurs entirely within the grain, concluding with the emergence of a new insect. This feeding activity reduces grain weight, germination capacity, and nutritional value (Yang et al., 2020; Patiño-Bayona et al., 2021). Additionally, weevil infestations create conditions that favor the growth of other insects and mycotoxigenic fungi, such as *Aspergillus*, *Penicillium*, and *Fusarium* (Hubert et al., 2018). The main hazard of these storage fungi is the

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production of mycotoxins (Hubert et al., 2018; Usseglio et al., 2020), which present notable risks to both human and animal health. Phosphine, perimiphos-methyl and deltamethrin are the main synthetic insecticides commonly used to protect stored grain against insects (Dianxuan, 2006). However, the use of these pesticides poses certain problems, including the emergence of resistance in insects, particularly *S. zeamais* (Boyer et al., 2012; Agrafioti et al., 2019; Attia et al., 2020), as well as the problem of toxic residues in food, which is harmful to human health and the environment (Lucini & Molinari, 2011). All these problems are making the use of synthetic insecticides critical. Consequently, it is crucial to find effective natural alternatives to control stored grain insect pests. EOs and their major compounds have emerged as promising alternatives to synthetic insecticides (Said-Al Ahl et al., 2017). Several studies have shown that EOs and their major compounds can eliminate insects that damage stored produce, such as *S. zeamais* and other pests (Spochacz et al., 2018; Yang et al., 2020). Thymol is one such bioactive compound that has proved highly effective in combating problems associated with insect attack (Plata-Rueda et al., 2022). It acts on insects primarily by inhibiting acetylcholinesterase (AChE) and altering nicotinic acetylcholine receptors in the central nervous system. These mechanisms lead to neuronal disruption and eventual mortality (Campos et al., 2018).

The aim of this research was to investigate the repellent and fumigant effects of thymol, as well as its insecticidal action against *S. zeamais* by direct and indirect contact methods. The research also evaluated the long-term protective effect of thymol, showing that grains treated and stored for 12 months under controlled storage conditions remained free from infestation and all kinds of degradation.

MATERIALS AND METHODS

***Rearing of S. zeamais*:** The national seeds marketing corporation (SONACOS) SA, of Morocco, provided us with maize infested with *S. zeamais* adults, which were used in our study. Four 1L glass containers were supplied with 500g of corn as a food source, which was infested with 50 adult weevils, then covered with muslin cloth. To facilitate population development, the containers were incubated at 30 °C with 60-70% relative humidity (RH), and a photoperiod of 16:8 (Light:Dark). Unsexed adults weevils aged 2-7 days old were used in subsequent experiment.

***Insecticidal agent*:** Thymol, the active compound used in this study, was sourced from Sigma-Aldrich (Steinheim, Germany). Thymol was prepared by dissolving in a suspension containing 0.2% agar in sterile distilled water, following the method of Remmal et al. (1993). This method allows the dispersion of EOs and their major components without the use of solvents, detergents or other excipients. The final concentration of thymol in the composition was 300 µL/mL.

***Repellent activity test*:** The repellent activity of thymol against *S. zeamais* was evaluated using the preferential area method on filter paper, as described by McDonald et al. (1970). Whatman No. 2 filter paper (9 cm in diameter) was cut into two equal halves and used in this experiment. Various concentrations of thymol (75, 150, and 300 µL/mL) were prepared from the stock solution. A micropipette was used to evenly apply 500 µL of each concentration one half of the filter paper, While the other half was treated with 500 µL of 0.2% agar as a control. The treated halves were air-dried for 5 min, re-joined, and secured with clear adhesive tape. Twenty insects were released into the center of each filter paper in a Petri dish (9 cm diameter). The number of insects in the treated (Nt) and control (Nc) areas was recorded after 1h, 2h, 4h, and 6h. Percentage repellency (PR) was calculated using the formula (McDonald et al., 1970).

$$\text{PR}\ (\%) = \frac{\text{Nc} - \text{Nt}}{\text{Nc} + \text{Nt}} * 100$$

Where PR (%) represents percentage repellency, Nc is the number of insects in control area, and Nt is the number of insects in the treated area.

***Fumigant activity test*:** The fumigation toxicity of thymol against *S. zeamais* adults was tested in 100 mL glass vials, following Shahinfar et al. (2021). Twenty unsexed adults (2-7 days old) were placed in each vial with 5g of corn as a food source. Pieces of Whatman N°. 2 filter paper (2.5 cm diameter), were affixed to the underside of the vial caps, and treated with 200 µL of thymol at various concentrations (0, 75, 150, and 300 µL/mL). A control treatment with 200 µL of 0.2 % agar was included. Vials were incubated at 30 °C, 60-70% RH, and a photoperiod of 16:8 h (Light: Dark) for 4 days. Mortality was recorded daily, and four replicates were performed for each treatment. Insects were considered dead if they showed no movement of body, heads, or antennae (Ouko et al., 2017).

Mortality was calculated using Abbott's correction formula (Abbott, 1925).

$$\text{Mortality}\ (\%) = \frac{\text{Mt} - \text{Mc}}{100 - Mc} * 100$$

Where Mt is mortality in treated group and Mc is the mortality in the control group.

***Topical contact toxicity test*:** The thymol's topical toxicity was assessed on *S. zeamais* adults using the method described by Plata-Rueda et al. (2020). The stock solution was diluted in 0.2% agar to achieve four concentrations (0, 0.03, 0.06 and 0.12 µL/insect). Using a micropipette, 0.2 µL of each dose was applied to the thorax of twenty unsexed adults of *S. zeamais*. After treatment, the weevils were transferred to Petri dishes and incubated at 30 °C with 60- 70% RH under a photoperiod of 16:8 h (Light: Dark). Mortality was recorded after 24h. Four replicates were conducted for each dose, and

mortality percentages were calculated using Abbott's correction formula (Abbott, 1925).

Toxicity test on treated grains

***Weevil mortality by contact with treated grains*:** This experiment involved the direct application of thymol to corn grains following the method of Alehegn et al. (2020). Fifty grams of grains in 100 mL vials were treated with various concentrations (0, 0.6, 1.2, and 1.8 µL/g of grain). After mixing for 1 min and allowing 10 min for drying, twenty unsexed adults were introduced to each vial. The vials, covered with muslin cloth to facilitate air circulation, were stored at 30°C with 60-70% RH under a 16:8 h light-dark cycle for 7 days. Insects were monitored daily; dead insects were removed, and survivors insects were returned to the vials. Four replicates were conducted for per treatment. Mortality was recorded daily, and calculated using Abbott's formula (Abbott, 1925).

***Long-term efficacy of thymol: grain weight Loss, holes formation, and inhibition rate of progeny insects after 12 months of storage*:** The vials from the toxicity test containing 50 g of wheat were maintained under the same incubation conditions (30 °C with 60-70% RH under a 16:8 h light-dark cycle) for 12 months. Live insects in the control group were removed prior to incubation. After storage, assessments were conducted for grain weight loss, percentage of holes, and inhibition rate of progeny insects:

Grain weight loss: Initial and final dry weights were measured using a precision balance. Weight loss was calculated using the formula of Wale and Mengie (2017):

$$\text{Weight loss (\%)} = \frac{\text{IDW} - \text{FDW}}{\text{IDW}} * 100$$

Where: IDW - initial dry weight, and FDW - final dry weight.

***Hole formation*:** After 12 months, the total grains and those with holes were counted. The percentage of holes (PH) was calculated using the formula of Wale and Mengie (2017):

$$\text{PH (\%)} = \frac{\text{TNGH}}{\text{TNG}} * 100$$

Where: PH - the percentage of holes, TNGH - total number of grains treated with holes, and TNG = total number of seeds.

***Progeny insects*:** 12 months after the application of a single thymol treatment, a head count of the number of emerging adults was carried out and the inhibition rate (IR) was calculated using the formula of Alkan and Ertürk (2020):

$$\text{IR (\%)} = \text{Cn} - \frac{\text{Tn}}{\text{Cn}} * 100$$

Where; IR %, inhibition rate; Cn, number of newly emerged adults in untreated replicates (control); Tn, number of newly emerged insects in treated replicates.

***Molecular docking*:** Molecular docking is an *in silico* study enabling the understanding of structural requirements, while focusing on the analysis of ligand-receptor interactions (Soukaina et al., 2023).

The X-ray crystal structure was retrieved from the PDB-RCSB database (PDB ID: 7E3H) at a resolution of 2.45 Å. The three-dimensional structure of thymol was obtained from the PubChem database in SDF format. Protein preparation was carried out using the "Protein preparation wizard" module, adding hydrogens, deleting water molecules and applying the Epik method (Soukaina et al., 2024). Ligands were optimized in the "LigPrep" module, retaining the default parameters. Docking was performed for ligands and receptors prepared with grids generated using SP docking precision, and binding energy was represented in kcal/mol. The visualization of the results was performed using Discovery Studio 2021 software.

***Statistical analysis*:** Biological data were analyzed using One-Way ANOVA followed by Tukey's multiple comparison test (ANOVA followed by Tukey's test) using Graph Pad Prism software (version 5.03). Results are expressed as mean values ± SEM (standard error of the mean). Differences were considered as significant at $p < 0.05$.

RESULTS

***Repellent activity test*:** The repellent activity of thymol against *S. zeamais* is demonstrated in Figure 1. The activity exhibited a dose-dependent increase. At a concentration of 300 µL/mL, the repellency percentage was relatively high (70%) after one hour of exposure. This effect increased to 82% after 4 hours, and reached 87% by the end of the experiment, showing a significant difference compared to other concentrations ($p < 0.05$). A similar repulsive activity was observed at concentrations of 75 and 150 µL/mL, where the repellency percentages were 70% and 72.5% after 4 and 6 hours, respectively.

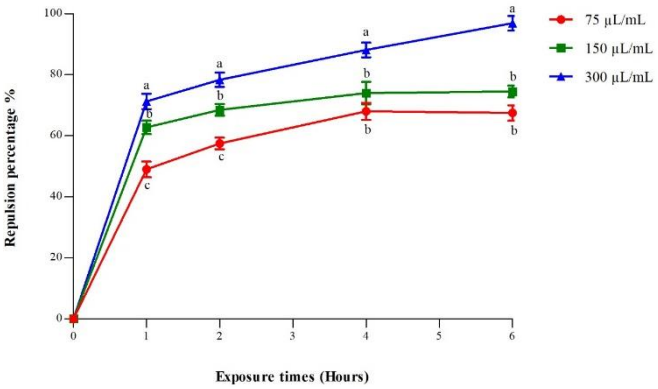

Figure 1. Percentage repellency of thymol against *S. zeamais*.

The results are expressed as means ± standard deviation, and values with different letters are significantly different ($p < 0.05$)

***Fumigant activity test*:** Figure 2 illustrates the fumigant activity of thymol against the corn weevil *S. zeamais*. The results demonstrated significant fumigant efficacy in a dose-dependent effect. At a concentration of 300 µL/mL, the

mortality reached 98% after 4 days of exposure, showing a consistently significant difference from the control ($p < 0.05$). At 150 µL/mL, the mortality rate was 13% by the end of the exposure period with a significant difference achieved only after the fourth day. In contrast, the 75 µL/mL concentration showed non-significant effects against *S. zeamais*, with a mortality rate not exceeding 5% even after four days of treatment. Overall, the highest mortality rate by fumigation was observed at the concentration of 300 µL/mL.

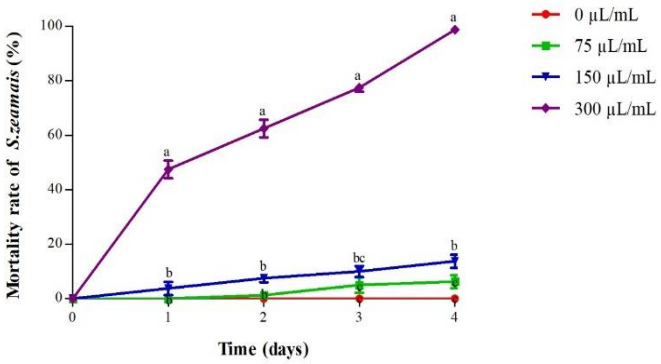

Figure 2. Fumigant activity of thymol against *S. zeamais*.
The results are expressed as means ± standard deviation, and values with different letters are significantly different ($p < 0.05$)

***Topical contact toxicity test*:** The results presented in Figure 3 illustrate the toxicity via direct contact on the thorax of insects 24 hours after exposure to the thymol. At the lowest dose of 0.03 µL/insect, the mortality rate was relatively low (less than 10%) but still showed a significant difference from the control group. At a dose of 0.06 µL/insect, mortality increased substantially, reaching 81%. Complete mortality was observed in insects treated with the highest dose of 0.12 µL/insect.

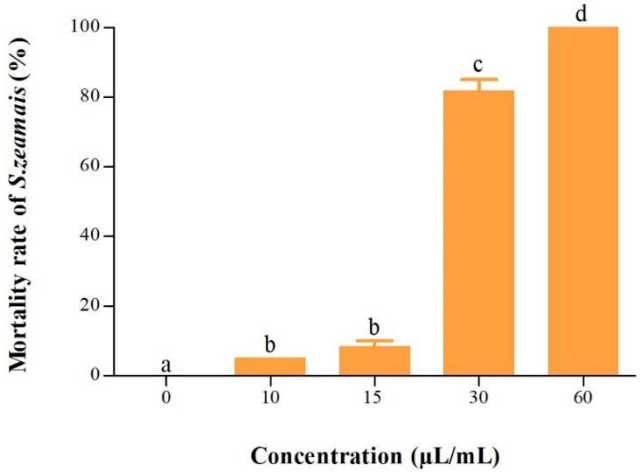

Figure 3. The results of topical contact toxicity of thymol against *S. zeamais*.
The results are expressed as means ± standard deviation, and values with different letters are significantly different ($p < 0.05$)

Toxicity test in treated grain

***Weevil mortality by contact with treated grain*:** The direct contact between *S. zeamais* and treated grains showed significant insecticidal activity, exhibiting a clear dose-response effect (Fig. 4). At a concentration of 0.6 µL/g, the mortality rate was about 3% on the first day, increased to 50% by the fourth day, and reached 98% by the end of treatment period. For the 1.2 µL/g concentration, the mortality rate was 13% on the first day of treatment, rising to 55% on the third day and achieving 100% after 7 days of exposure. At the highest tested concentration of 1.8 µL/g, the mortality rate exceeded 50% after 2 days of exposure and reached 100% by the sixth day. No mortality was observed in control groups. From the third day of exposure onward, the difference in mortality between untreated and treated grains, regardless of the concentration, was highly significant ($p < 0.001$).

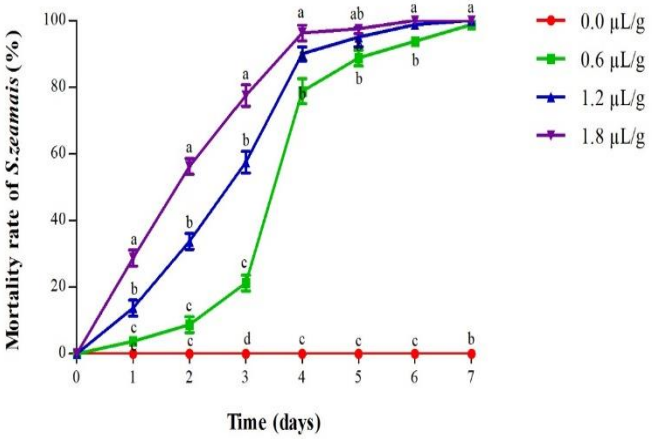

Figure 4. Mortality rate of *S. zeamais* adults exposed to thymol-treated grain.
The results are expressed as means ± standard deviation, and values with different letters are significantly different ($p < 0.05$)

***Long-term efficacy of a natural composition: grain weight Loss, holes formation and inhibition rate of progeny insects after 12 months of storage*:** The results presented in Table 1 demonstrate the protective effect of thymol on treated grains over a 12-month period. It was observed that the percentage of holes in the control was approximately 89%, which significantly decreased to 1% for the batch treated with a concentration of 0.6 µL/g. For the other concentrations used in the treatment (1.2 and 1.8 µL/g), holes were completely absent. Weight loss was significantly higher in the control grains (37%) compared to the treated grains, where the percentage of loss was 0% ($p < 0.0001$). Regarding progeny insects, thymol completely inhibited the emergence of progeny insects at a concentration of 1.2 µL/g, while the concentration of 0.6 µL/g achieved a 99% inhibition rate.

Table 1. Weight loss, percentage of holes, and inhibition rate of progeny insects 12 months after *S. zeamais* adults exposed to the grains treated with different concentrations of thymol.

	Percentage of holes (%)	Weight loss (%)	Inhibition rate of progeny insects (%)
0.0 µL/g	88.59±3.17^{a}	37.14±4.79^{a}	0.00±0.00^{a}
0.6 µL/g	0.89±0.59^{b}	0.00±0.00^{b}	99.65±0.50^{b}
1.2 µL/g	0.00±0.00^{b}	0.00±0.00^{b}	100.00±0.00^{b}
1.8 µL/g	0.00±0.00^{b}	0.00±0.00^{b}	100.00±0.00^{b}

The results are expressed as means ± standard deviation, and values with different letters are significantly different ($p < 0.05$).

The photograph in Figure 5 illustrates the preservation of corn grains 12 months after the treatment with thymol. For the batches treated at a concentration of 1.2 µL/g and higher, the grains remained intact throughout the 12 months of storage, showing no signs of deterioration. In contrast, the control lot displayed significant grain deterioration, characterized by the presence of holes, the emergence of new insects, and a noticeable accumulation of flour.

Untreated corn

Treated corn (1.2 µL/g)

Figure 5. Untreated and treated corn grains with 1.2 µL/g of thymol after 12 months of storage.

***Molecular docking*:** Figure 6 shows the docking scores of thymol against the Acetylcholinesterase protein (PDB ID: 7E3H). Thymol showed the formation of two conventional hydrogen bond with the amino acid residues: Gly-121 (2.95 Å) and Glu-202 (1.63 Å), with a binding energy of -7.291 kcal/mol.

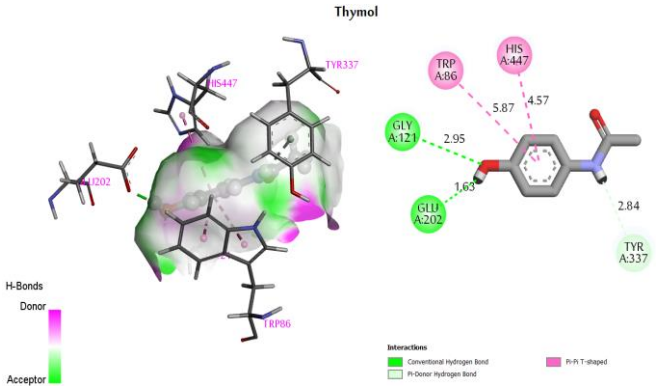

Figure 6. 2D and 3D visualisation of docking results of thymol in the site active of the protein (PDB ID: 7E3H).

DISCUSSION

Numerous studies have demonstrated the insecticidal activity of EOs and their major compounds (Campolo et al., 2018; Avila et al., 2023). Thymol is one of the most effective major compounds with potent insecticidal activity against many insect species (Pengsook et al., 2022; Kumrungsee et al., 2022), as well as the corn weevil (Rodríguez et al., 2022). The present work was aimed at evaluating the repellent, fumigant and insecticidal properties of thymol against adults of *S. zeamais*, as well as its ability to protect grains against weevils over a long storage period of up to 12 months. In addition, an *in silico* analysis was carried out to assess the effect of thymol on acetylcholinesterase.

Thymol was dispersed in a 0.2% agar solution. This is a eco-friendlier and more sustainable alternative to traditional solvents and detergents, which can reduce the efficacy of EOs and their main compounds. Remmal et al. (1993) found that detergents and solvents reduced the antimicrobial properties of EOs. Insects are naturally attracted to the volatile compounds emitted by wheat grains. However, EO treatments can alter this olfactory profile (Germinara et al., 2015), hence our idea to assess the repellent activity of thymol and its ability to alter these odors to reduce the chances of weevils detecting treated grains. To realize this test, we adopted the preferable area method described by McDonald et al. (1970). The results obtained showed that thymol has a significant repellent activity at concentrations ranging from 150 µL/mL to 300 µL/mL), with the strongest effects observed at 300 µL/mL. Several studies have ranked thymol as one of the most promising repellents, with the highest repellent activity (Da

Silva et al., 2024; Arif & Guarino, 2024). Another study on *Lippia sidoides* EO and its majority compound, thymol, shows its repellent activity on the corn weevil *S. zeamais* (Oliveira *et al*., 2018). This effect could be linked to the detection of thymol by the insects' olfactory organs, which activate flight behaviors (Missbach et al., 2014). Correa et al. (2015) conducted a study on locomotor and physiological responses induced by clove and cinnamon EOs on the corn weevil *S. zeamais*, showing that *S. zeamais* populations probably recognize EO components and increase their locomotor activities as an escape strategy (Missbach et al., 2014). The fumigant activity of thymol was evaluated, following the method described by Shahinfar et al. (2021). The results obtained in this test demonstrated significant mortality rates at a concentration of 300 µL/mL, achieving 98% mortality within four days. Thymol can penetrate insects through the spiracles (Gomes & Favero, 2011). It then spreads into the trachea and tracheoles and binds to hemolymph components (Upadhyay & Ahmad, 2011), that explains the toxicity of thymol by fumigation on *S. zeamais* populations.

These encouraging results led us to explore the insecticidal action of thymol using two approaches. The direct contact method, as described by Plata-Rueda et al. (2020), applied the treatment directly to the insect's thorax, resulting in total mortality at a dose of 0.12 µL/insect within 24 hours. The indirect method that involves treating the grains before introducing them to live adult weevils, following protocols by Alehegn et al. (2020). This approach demonstrated dose-dependent insecticidal activity. The concentrations of 1.2 and 1.8 µL/g resulted in more than 50% mortality, within 3 days and total mortality by the seventh day. Studies have established the high toxicity of oregano EO and its major compound thymol to insects like *S. granarius* (Plata-Rueda et al., 2022; Houiat et al., 2025), acting primarily through the inhibition of acetylcholinesterase (AChE) and interaction with nicotinic acetylcholine receptors in the central nervous system, which leads to mortality (Campos et al., 2018). Additionally, thymol affects GABA receptors, disrupting synapse function and further impairing insect's cellular activities (Priestley et al., 2003; Regnault-Roger et al., 2012). Monoterpenes, including thymol, also potentially enhance the efficacy of other molecules by inhibiting cytochromes P450 (Lee et al., 2001; Ketoh et al., 2002).

In our knowledge, this is the first study to extend corn grains observation to 12 months of storage, affirming the thymol's long-term protective efficacy by a single treatment against corn weevils. The choice of a 12-month period aligns with typical grain storage durations, crucial for reducing costs and enhancing food security in developing countries.

After 12 months, untreated grains showed a significant deterioration with 88.59% of holes and 37% reduction in weight. In contrast, grains treated with the 0.6 µL/g concentration of thymol maintained their integrity with negligible insect emergence, resulting in a minimal 0.89% of holes and no weight loss. Higher concentrations of 1.6 and 1.8 µL/g prevented hole formation entirely and preserved grain weight.

Insecticides often target critical biological processes in insects, including inhibition of acetylcholinesterase (AChE). AChE inhibitors, such as organophosphates, prevent the degradation of acetylcholine, leading to continuous transmission of nerve signals, overstimulation, paralysis and rapid death of the insect (Harmouzi et al., 2024). In our study *in silico* analysis was carried out to examine the interaction between thymol and the enzyme acetylcholinesterase from *S. zeamais*. Molecular docking simulations, using 3D visualizations, demonstrate that thymol bound to acetylcholinesterase generating various intermolecular interactions with very low binding energy (-7.291 kcal/mol). This theoretical analysis enables us to predict the activity of thymol and this potential target, while confirming its powerful insecticidal effect and highlighting a promising interaction. This approach provides a solid basis for the experimental phase. These observations underline the strong potential of thymol as a natural insecticidal agent for preventive and curative applications, offering protection for up to 12 months with a single treatment, providing a sustainable solution for post-harvest protection, particularly in contexts where grain quality preservation and treatment safety are fundamental considerations.

***Conclusion*:** In conclusion, our research confirms the effectiveness of thymol in repelling, fumigating, and killing insects, offering a sustainable alternative to conventional insecticides for protecting stored grains over long periods. A thymol-based bio-insecticide mitigates the common drawbacks of traditional insecticides, such as toxicity and resistance development.

***CRediT author statement*:** A.H. conceptualized the study, collected the data, and drafted and finalized the manuscript; M.O. and S.H. contributed to the experimental design and revised the manuscript; S.A.A. and O.Z. were involved in data analysis and research interpretation; M.K. and C.M. were edited the manuscript to the final form; A.R. validated, edited the finale manuscript and supervised the work. All the authors have read and approved the final manuscript.

***Conflicts of interest*:** The authors declare that they have no conflicts of interest.

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***Ethical statement*:** N/A

***Availability of data and material*:** All data is published in this research article.

***SDGs addressed*:** Zero Hunger; Good Health and Well-being; Responsible Consumption and Production

***Policy referred*:** FAO's Code of Conduct on Pesticide Management (FAO & WHO); The United Nations Sustainable Development Goals (SDGs); International Plant Protection Convention (IPPC)

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